

Variant: *NM_000546.6(TP53):c.733G>A (p.Gly245Ser)*

Version: 1.1

CA000367 [↗](#)

12365 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))

Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: ed201831-1d8d-4c6d-ad13-1055f8d3407b

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HGVS expressions

NM_000546.6:c.733G>A

NM_000546.6(TP53):c.733G>A (p.Gly245Ser)

NC_000017.11:g.7674230C>T

CM000679.2:g.7674230C>T

NC_000017.10:g.7577548C>T

CM000679.1:g.7577548C>T

NC_000017.9:g.7518273C>T

NG_017013.2:g.18321G>A

ENST00000503591.2:c.733G>A

ENST00000508793.6:c.733G>A

ENST00000509690.6:c.337G>A

ENST00000514944.6:c.454G>A

ENST00000604348.6:c.712G>A

ENST00000269305.9:c.733G>A

ENST00000269305.8:c.733G>A

ENST00000359597.8:c.733G>A

ENST00000413465.6:c.733G>A

ENST00000420246.6:c.733G>A

ENST00000445888.6:c.733G>A

ENST00000455263.6:c.733G>A

ENST00000504290.5:c.337G>A

ENST00000504937.5:c.337G>A

ENST00000509690.5:c.337G>A

ENST00000510385.5:c.337G>A

ENST00000514944.5:c.454G>A

ENST00000610292.4:c.616G>A

ENST00000610538.4:c.616G>A

ENST00000610623.4:c.256G>A

ENST00000615910.4:c.700G>A

ENST00000617185.4:c.733G>A

ENST00000618944.4:c.256G>A

ENST00000619186.4:c.256G>A

ENST00000619485.4:c.616G>A

ENST00000620739.4:c.616G>A

ENST00000622645.4:c.616G>A

ENST00000635293.1:c.616G>A

NM_000546.5:c.733G>A

NM_001126112.2:c.733G>A
NM_001126113.2:c.733G>A
NM_001126114.2:c.733G>A
NM_001126115.1:c.337G>A
NM_001126116.1:c.337G>A
NM_001126117.1:c.337G>A
NM_001126118.1:c.616G>A
NM_001276695.1:c.616G>A
NM_001276696.1:c.616G>A
NM_001276697.1:c.256G>A
NM_001276698.1:c.256G>A
NM_001276699.1:c.256G>A
NM_001276760.1:c.616G>A
NM_001276761.1:c.616G>A
NM_001276695.2:c.616G>A
NM_001276696.2:c.616G>A
NM_001276697.2:c.256G>A
NM_001276698.2:c.256G>A
NM_001276699.2:c.256G>A
NM_001276760.2:c.616G>A
NM_001276761.2:c.616G>A
NM_001126112.3:c.733G>A
NM_001126113.3:c.733G>A
NM_001126114.3:c.733G>A
NM_001126115.2:c.337G>A
NM_001126116.2:c.337G>A
NM_001126117.2:c.337G>A
NM_001126118.2:c.616G>A
NM_001276695.3:c.616G>A
NM_001276696.3:c.616G>A
NM_001276697.3:c.256G>A
NM_001276698.3:c.256G>A
NM_001276699.3:c.256G>A
NM_001276760.3:c.616G>A
NM_001276761.3:c.616G>A

Pathogenic

Met criteria codes 7

- PP4_Moderate
- PS2_Moderate
- PP3
- PS3
- PS4
- PM1
- PM2_Supporting

Not Met criteria codes 10

- BP4
- BS2
- BS1
- BS4
- BS3
- PP1
- PS1
- BA1
- PM5
- PVS1

Evidence Links 0

Expert Panel

TP53 VCEP

Criteria Specification Information

[Criteria Specification:](#) ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.733G>A variant in TP53 is a missense variant predicted to cause substitution of glycine by serine at amino acid 245 (p.Gly245Ser). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with a strongly LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; Internal lab contributor: SCV000184981.8). This variant has been reported in an additional individual meeting Classical criteria and 11 individuals meeting Revised Chompret criteria. Based on this evidence, this variant scores 8 total points meeting the TP53 VCEP phenotype scoring criteria of ≥ 8 points. (PS4_Very Strong; PMIDs: 11370630, 32156018, 32888145, 33245408, 34670578, 35974385, 20522432, 24122735, Internal lab contributor: SCV000184981.8). At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, Internal lab contributors: SCV000184981.8). This variant has an allele frequency of 0.000002543 (3/1179926 alleles) in the European (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PMIDs: 12826609, 30224644, 29979965) (PS3). This variant resides within a codon (NM_00546.4: 175, 245, 248, 249, 273, 282) of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PMID: 8023157) (PM1). Computational predictor scores (BayesDel = 0.5536; Align GVGD = Class C55) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3). In summary, this variant meets the criteria to be classified as Pathogenic for Li Fraumeni Syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS2_Moderate, PS4_Very Strong, PP4_Moderate, PM2_Supporting, PS3, PM1, PP3. (Bayesian Points: 20; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

PP4_Moderate			At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, Internal lab contributors: SCV000184981.8).
PS2_Moderate			This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with a strongly LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; Internal lab contributor: SCV000184981.8).
PP3			Computational predictor scores (BayesDel = 0.5536; Align GVGD = Class C55) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3).
PS3			In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PMIDs: 12826609, 30224644, 29979965) (PS3).
PS4			PS4_VERY STRONG APPLIED This variant has been reported in 1 individual meeting Classical criteria and 11 individuals meeting Revised Chompret criteria. Based on this evidence, this variant scores 8 total points meeting the TP53 VCEP phenotype scoring criteria of ≥ 8 points. (PS4_Very Strong; PMIDs: 11370630, 32156018, 32888145, 33245408, 34670578, 35974385, 20522432, 24122735, Internal lab contributor: SCV000184981.8).
PM1			This variant resides within a codon (NM_00546.4: 175, 245, 248, 249, 273, 282) of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PMID: 8023157) (PM1).
PM2_Supporting			This variant has an allele frequency of 0.000002543 (3/1179926 alleles) in the European (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).

Not Met criteria codes

BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			Two different missense variants (c.733G>C, c.733G>T) in the same codon have been reported (ClinVar IDs 376604, 12349). However, the variants have not yet been curated to determine if they would be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not evaluated).
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 

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